Blood Pressure Variability in Obstructive Sleep Apnoea: Data from 4 Randomised Controlled CPAP Withdrawal Trials

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Abstract: BACKGROUND Increased daytime blood pressure variability (BPV) is associated with cardiovascular risk. Preliminary data suggest that obstructive sleep apnoea (OSA) might contribute to increased daytime BPV. OBJECTIVE The aim of this study was to evaluate the effect of continuous positive airway pressure (CPAP) therapy withdrawal on daytime BPV. METHODS A total of 183 patients previously diagnosed with OSA and treated with CPAP were randomised to either continue or withdraw from CPAP within 4 trials. Office morning BP was measured in triplicate at baseline and at follow-up (day 14). In addition, the participants performed BP measurements at home on a daily basis (days 1-13). The main outcome of interest was the treatment effect on within-visit BPV expressed as the standard deviation (SD) of the triplicate measurements. Additional outcomes included morning home BPV and day-to-day home BPV. RESULTS Within-visit variability in systolic BP significantly increased in response to recurrence of OSA in the CPAP withdrawal group (difference between groups in SD of systolic BPV, +1.14 mm Hg, 95% CI +0.20/+2.09, p = 0.02). There was no statistically significant effect on within-visit variability in diastolic BP (p = 0.38) or heart rate (p = 0.07). Neither morning home BP variability (systolic BPV, p = 0.81; diastolic BPV, p = 0.46) nor day-to-day variability in home BP measurements (systolic BPV, p = 0.61; diastolic BPV, p = 0.58) differed significantly between the groups. CONCLUSION CPAP withdrawal results in a minor increase in within-visit variability in office systolic BP, but it has no effect on home BPV or day-to-day BPV. Although the treatment effect may be blunted by antihypertensives, it is unlikely that OSA contributes to cardiovascular risk via elevated daytime BPV.

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Blood Pressure Variability in Obstructive Sleep Apnoea: Data from 4 Randomised Controlled CPAP Withdrawal Trials

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Keywords
Obstructive sleep apnoea · Continuous positive airway pressure · Blood pressure variability

Abstract
Background: Increased daytime blood pressure variability (BPV) is associated with cardiovascular risk. Preliminary data suggest that obstructive sleep apnoea (OSA) might contribute to increased daytime BPV. ***Objective:*** The aim of this study was to evaluate the effect of continuous positive airway pressure (CPAP) therapy withdrawal on daytime BPV. ***Methods:*** A total of 183 patients previously diagnosed with OSA and treated with CPAP were randomised to either continue or withdraw from CPAP within 4 trials. Office morning BP was measured in triplicate at baseline and at follow-up (day 14). In addition, the participants performed BP measurements at home on a daily basis (days 1–13). The main outcome of interest was the treatment effect on within-visit BPV expressed as the standard deviation (SD) of the triplicate measurements. Additional outcomes included morning home BPV and day-to-day home BPV. ***Results:*** Within-visit variability in systolic BP significantly increased in response to recurrence of OSA in the CPAP withdrawal group (difference between groups in SD of systolic BPV, +1.14 mm Hg, 95% CI +0.20/+2.09, $p = 0.02$). There was no statistically significant effect on within-visit variability in diastolic BP ($p = 0.38$) or heart rate ($p = 0.07$). Neither morning home BP variability (systolic BPV, $p = 0.81$; diastolic BPV, $p = 0.46$) nor day-to-day variability in home BP measurements (systolic BPV, $p = 0.61$; diastolic BPV, $p = 0.58$) differed significantly between the groups. ***Conclusion:*** CPAP withdrawal results in a minor increase in within-visit variability in office systolic BP, but it has no effect on home BPV or day-to-day BPV. Although the treatment effect may be blunted by antihypertensives, it is unlikely that OSA contributes to cardiovascular risk via elevated daytime BPV.

Introduction

Obstructive sleep apnoea (OSA) has been identified as a common factor associated with hypertension and cardiovascular disease (CVD), although potential causal mechanisms have not been fully elucidated [1]. The prevalence of OSA is likely to further increase as a result of increasing obesity [2]. Observational and population-based epidemiological studies have shown that untreated moderate-to-severe OSA is associated with hypertension and adverse cardiovascular outcome [3–7]. However, randomised controlled trials on the effects of continuous

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positive airway pressure (CPAP) therapy have so far only established a causal association between OSA and diurnal hypertension [8].

Hypertension is an established risk factor for CVD [9]. In recent years, not only sustained blood pressure (BP) elevation itself but also BP variability (BPV) have been recognised as important predictors of CVD [10–12]; there seems to be a connection between high BPV and increased cardiovascular morbidity and mortality, even in patients with well-controlled BP [11–14]. These findings have been linked to alteration of vascular reactivity due to, amongst other factors, increased arterial stiffness and endothelial dysfunction [15–17]. Similarly, impaired endothelial function has been observed in OSA patients [18–20], possibly linking the underlying pathophysiology of OSA and elevated BPV. Furthermore, the consequences of OSA involve numerous mechanisms such as autonomic dysregulation and increased sympathetic activity, thus linking OSA to elevated BP levels and potentially to increased BPV [21, 22]. One might, therefore, hypothesise that not only elevated BP levels but also increased BPV may be caused by OSA and contribute to the associated adverse cardiovascular outcomes.

An association between the severity of OSA and BPV has previously been described in physiologic and observational studies [23, 24]. While it could be shown that CPAP therapy effectively abolishes OSA [25], improves endothelial function [26, 27], and reduces BP [8], there are controversial data on the effect of CPAP therapy on daytime BPV [28, 29]. Although there have been studies on the association of OSA with BPV, evidence from randomised controlled interventional trials is missing.

Short-term CPAP therapy withdrawal has been shown to result in the recurrence of OSA and its consequences such as increased BP, sympathetic activity, and impaired endothelial function [20, 30]. Therefore, we considered this study design suitable to evaluate the effects of CPAP withdrawal on BPV. We hypothesised that the recurrence of OSA in response to therapy withdrawal would result in an increase in within-visit BPV as well as in short-term morning home BPV and intermediate-term day-to-day BPV.

Subjects and Methods

Trial Design and Intervention

Four randomised controlled trials, which allocated CPAP-treated patients to either continue or withdraw from CPAP for 2 weeks, were conducted in Zurich and Oxford between 2010 and 2015 [20, 30–32]. Patients registered in the sleep database of the Sleep Disorders Centre and Pulmonary Division of the University Hospital Zurich, Zurich, Switzerland, and of the Centre for Respiratory Medicine, Oxford, UK, were recruited. Baseline examinations on therapeutic CPAP therapy were performed in both study arms. The morning after the baseline sleep studies, the patients were randomly assigned to either continue therapeutic CPAP or withdraw from CPAP (subtherapeutic sham CPAP or non-therapeutic nasal device) and returned 2 weeks later for the follow-up sleep study on the assigned treatment. Morning BP was measured daily in triplicate during the study period. The studies were approved by the research ethics committees in Zurich (EK-1600, KEK-ZH-2012-051) and Oxford (11/NW/0370). Written informed consent was obtained from all participants. The trials were registered prior to commencement (ClinicalTrials.gov NCT01332175, NCT01797653, and NCT02050425; controlled-trials.com: ISRCTN 93153804).

Participants

Subjects with known OSA were recruited from the Sleep Disorders Centre and Pulmonary Division of the University Hospital Zurich and from the Centre for Respiratory Medicine in Oxford. Patients aged 20–75 years with an oxygen desaturation index (ODI) of ≥10/h [20, 30] or 20/h [31, 32] in their in-laboratory sleep study at the time of diagnosis were eligible if they had been treated with CPAP for at least 1 year (compliance of ≥4 h/night) and currently had an ODI >10/h [20, 30] or >20/h [31, 32] in a nocturnal pulse oximetry assessment on the last night of a 4-night period off CPAP treatment. Exclusion criteria were ventilatory failure, Cheyne-Stokes respiration, unstable or untreated vascular disease, inadequately controlled arterial hypo- or hypertension, professional driving, and a previous traffic accident associated with sleepiness.

Outcomes

The main outcome of interest was the treatment effect on within-visit BPV (standard deviation [SD] of 3 repeated office BP measurements [day 0 and day 14]). Other outcomes of interest were short-term morning home BPV (mean daily SD of 3 repeated home BP measurements over 2 weeks: $[SD_{triplet1} + SD_{triplet2} + \ldots + SD_{triplet13}]/13$) and intermediate-term day-to-day BPV (SD of daily mean home BP over 2 weeks: SD of $[BP_1 + BP_2 + \ldots + BP_{13}]$), as well as heart rate (HR) variability over the whole study period and effects on sleep apnoea severity (ODI).

After the baseline and follow-up sleep studies, morning office BP and HR were measured in triplicate (1-min intervals) with a validated standard digital automatic monitor (Omron Healthcare Co., Kyoto, Japan). In addition, the patients measured their home morning BP and HR in triplicate with the same device each day during the study period. The measurements were performed according to a standardised protocol: in a sitting position after a period of rest of ≥5 min, immediately after getting up, before breakfast, and before intake of antihypertensive drugs, with 1-min intervals between the 3 measurements. The sleep studies and therapy devices (CPAP, subtherapeutic CPAP, and ineffective nasal devices) have previously been described [20, 30–32].

Randomisation and Blinding

The methods of randomisation and blinding have been reported previously [20, 30–32]. The patients and investigators were blinded to treatment allocation.

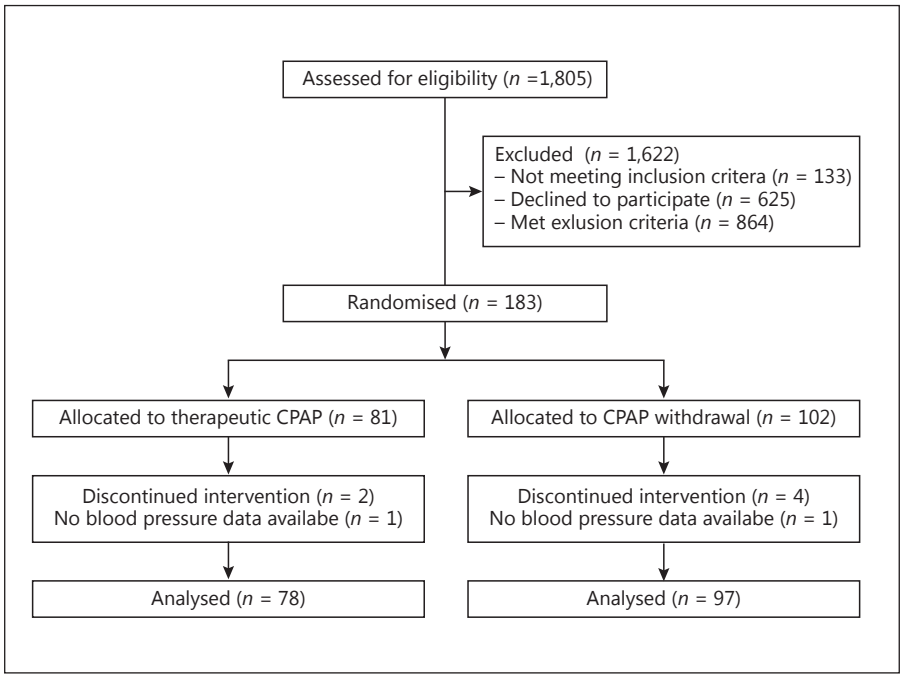

Fig. 1. Patient selection flow chart.

Statistical Methods

A per-protocol analysis was performed. The Kolmogorov-Smirnov test was used to test for normality of data distribution. For the main outcome of interest, between-group differences in change of within-visit BPV from baseline to follow-up were adjusted for baseline differences using linear regression models. For the additional outcomes, group differences between the patients randomised to continue and those randomised to withdraw from therapeutic CPAP were analysed with independent *t* tests for normally distributed and with Mann-Whitney U tests for non-normally distributed data. Analyses were conducted at a 2-sided significance level of <0.05. Statistica (version 12 for Windows; StatSoft Inc., Tulsa, OK, USA) was used for the statistical analyses.

Results

Participants

Of the 183 participants randomised to either continue therapeutic CPAP ($n = 81$) or withdraw from CPAP ($n = 102$), 175 completed the trial and provided BP data (Fig. 1). Two patients in the therapeutic CPAP and 4 patients in the withdrawal group discontinued the intervention. One participant in each group did not measure BP on a daily basis. Recruitment for the first trial [20] started in August 2009 and the last patient's visit [32] took place in August 2015. The baseline characteristics of the 2 treatment groups were comparable and are shown in Table 1.

Table 1. Baseline patient characteristics

	Therapeutic CPAP ($n = 78$)	CPAP withdrawal ($n = 97$)
Age, years	63.4±7.9	63.5±8.9
Male sex, *n* (%)	64 (82)	81 (83.5)
BMI	33.6±5.8	33.5±5.9
Neck circumference, cm	44.1±4.1	44.0±4.1
Never smoker, *n* (%)	38 (48.7)	39 (40.2)
Current smoker, *n* (%)	9 (11.5)	12 (12.4)
Former smoker, *n* (%)	31 (39.7)	46 (47.4)
Hypertension, *n* (%)	50 (64.1)	74 (76.3)
Mean number of antihypertensive drugs	1.4±1.4	1.6±1.4
Calcium antagonist, *n* (%)	19 (24.4)	30 (30.9)
Beta-blocker, *n* (%)	19 (24.4)	24 (24.7)
ACE inhibitor or ARB, *n* (%)	40 (51.3)	60 (61.9)
Diabetes, *n* (%)	19 (24.4)	24 (24.7)
Dyslipidaemia, *n* (%)	31 (39.7)	36 (37.1)
Original AHI, events/h	44.0±21.5	43.6±20.1
Original ODI, events/h	37.3±18.6	37.6±18.0
Original ESS score	13.8±3.3	13.9±3.7

Data are presented as means ± standard deviation unless otherwise mentioned. CPAP, continuous positive airway pressure; BMI, body mass index; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AHI, apnoea-hypopnoea index; ODI, oxygen desaturation index; ESS, Epworth Sleepiness Scale.

Table 2. Treatment effects on within-visit office blood pressure and heart rate variability

	Therapeutic CPAP (n = 78)		CPAP withdrawal (n = 97)		Treatment effect[1]		
	baseline	follow-up	baseline	follow-up	difference in change between groups	95% CI	p value
SD office SBP, mm Hg	4.55 (2.90)	4.37 (2.19)	4.88 (2.59)	5.52 (3.69)	+1.14	+0.20, +2.09	0.02
SD office DBP, mm Hg	3.26 (2.26)	3.48 (2.44)	3.04 (1.93)	3.82 (2.91)	+0.36	−0.45, +1.18	0.38
SD office HR, bpm	2.38 (2.05)	1.98 (1.79)	1.86 (1.36)	2.58 (2.72)	+0.67	−0.05, +1.39	0.07

Data are presented as means (SD) unless otherwise mentioned. CPAP, continuous positive airway pressure; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate. [1] Treatment effect adjusted for baseline differences.

Table 3. Longitudinal short- and intermediate-term home blood pressure and heart rate variability (days 1–13)

	Therapeutic CPAP (n = 78)	CPAP withdrawal (n = 97)	Difference between groups	95% CI	p value
Short-term morning home BP and HR variability (days 1–13)[1]					
SD SBP, mm Hg	4.97 (1.57)	5.03 (1.42)	+0.06	−0.39, +0.50	0.81
SD DBP, mm Hg	3.37 (1.09)	3.50 (1.20)	+0.13	−0.21, +0.48	0.46
SD HR, bpm	2.19 (1.01)	2.32 (1.19)	+0.13	−0.20, +0.47	0.43
Intermediate-term day-to-day home BP and HR variability (days 1–13)[2]					
SD SBP, mm Hg	6.88 (2.45)	7.06 (2.33)	+0.19	−0.53, +0.90	0.61
SD DBP, mm Hg	4.73 (1.70)	4.59 (1.53)	−0.14	−0.62, +0.35	0.58
SD HR, bpm	4.73 (2.58)	4.99 (2.35)	+0.26	−0.48, +0.99	0.49

Data are presented as means (SD) unless otherwise mentioned. CPAP, continuous positive airway pressure; BP, blood pressure; HR, heart rate; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure. [1] Mean daily SD of 3 repeated home BP measurements over 2 weeks: $(SD_{triplet1} + SD_{triplet2} + \ldots + SD_{triplet13})/13$. [2] SD of daily mean home BP over 2 weeks: SD of $(BP_1 + BP_2 + \ldots + BP_{13})$.

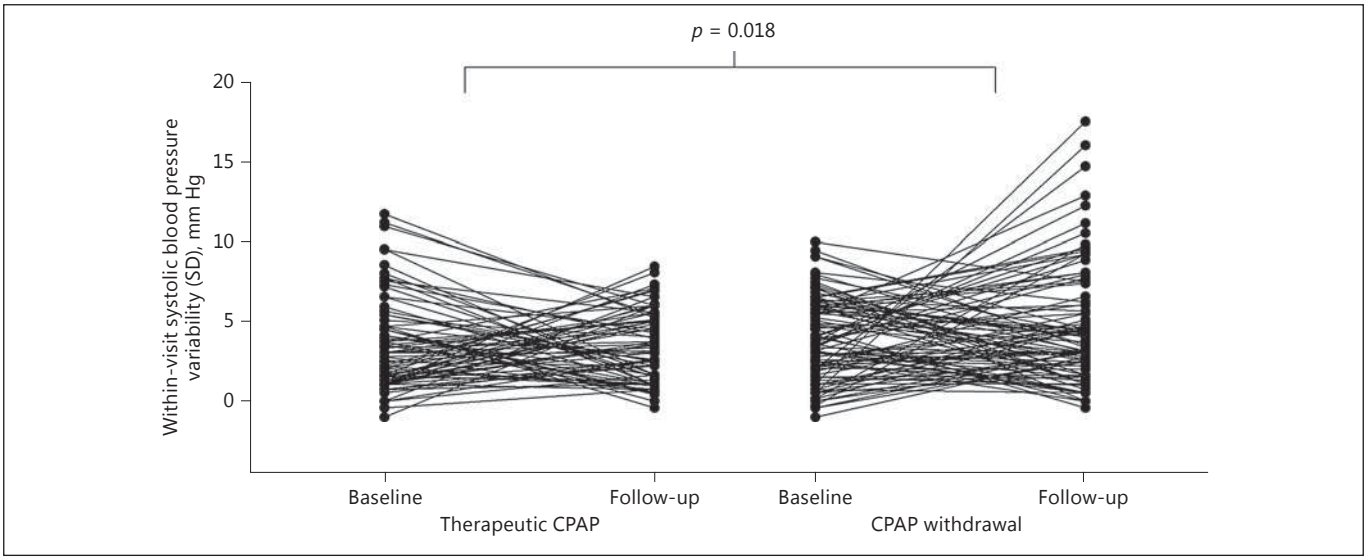

Fig. 2. Individual plots showing changes in within-visit blood pressure variability from baseline to follow-up in the group continuing therapeutic CPAP (left) and in the group withdrawn from CPAP therapy (right). CPAP, continuous positive airway pressure; SD, standard deviation.

Table 4. Treatment effects on OSA severity and daytime sleepiness

	Therapeutic CPAP (n = 78)		CPAP withdrawal (n = 84)		Treatment effect		
	baseline	follow-up	baseline	follow-up	difference in change between groups	95% CI	p value
AHI	2.4 (2.3)	3.2 (3.8)	2.8 (3.4)	33.1 (19.3)	+29.4	25.1, 33.7	<0.001
ODI	2.9 (4.0)	2.9 (3.6)	3.3 (3.9)	34.4 (19.3)	+31.1	26.9, 35.4	<0.001
ESS	7.2 (3.5)	7.0 (4.0)	7.6 (3.6)	9.5 (4.4)	+2.1	1.2, 2.9	<0.001

Data are presented as means (standard deviation) unless otherwise mentioned. OSA, obstructive sleep apnoea; CPAP, continuous positive airway pressure; AHI, apnoea-hypopnoea index (in events/h); ODI, oxygen desaturation index (in events/h); ESS, Epworth Sleepiness Scale (in points; max. 24 points).

Treatment Effect on Within-Visit Variability in BP and HR

CPAP withdrawal was associated with a statistically significant increase in within-visit variability in office systolic BP (between-group change in SD, +1.14 mm Hg, 95% CI +0.20/+2.09, p = 0.02), whereas it had no effect on variability in office diastolic BP (+0.36 mm Hg, 95% CI –0.45/+1.18, p = 0.38) compared with continuing therapeutic CPAP (Table 2; Fig. 2). There was a trend towards higher within-visit HR variability in the CPAP therapy withdrawal group compared to the group continuing therapeutic CPAP (between-group change in SD, +0.67 bpm, 95% CI –0.05/+1.39, p = 0.07) (Table 2).

Longitudinal Variability in Morning Home BP and HR

Short-term variability in neither systolic home BP (difference between groups in SD, 0.06 mm Hg, 95% CI –0.39/+0.50, p = 0.81) nor diastolic home BP (difference between groups in SD, +0.13 mm Hg, 95% CI –0.21/+0.48, p = 0.46) or HR (difference between groups in SD, +0.13 bpm, 95% CI –0.20/+0.47, p = 0.43) differed significantly between the 2 treatment groups over the study period (Table 3; Fig. 3).

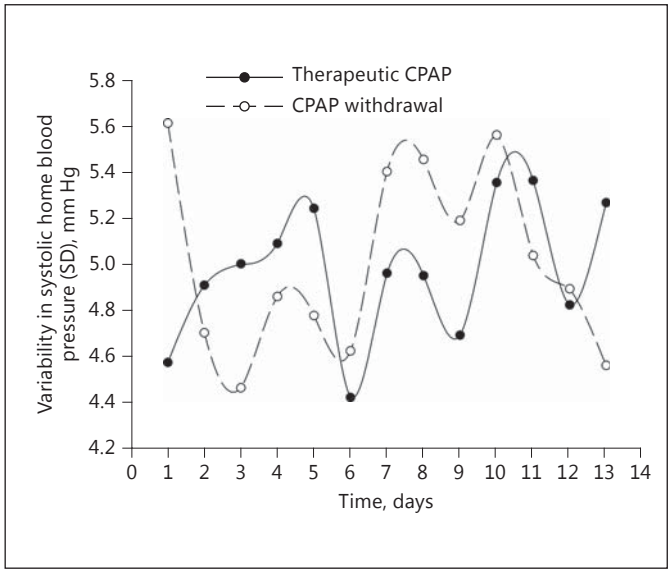

Fig. 3. Short-term variability in morning home systolic blood pressure after randomisation over the study period compared between the 2 groups. Each point represents the SD of a triplicate measurement of systolic home blood pressure (group mean) over 13 days after randomisation. CPAP, continuous positive airway pressure; SD, standard deviation.

Longitudinal Day-to-Day Variability in Home BP and HR

Day-to-day variability in systolic BP (difference between groups in SD, +0.19 mm Hg, 95% CI –0.53/+0.90, p = 0.61), diastolic BP (difference between groups in SD, –0.14 mm Hg, 95% CI –0.62/+0.35, p = 0.58), and HR (difference between groups in SD, +0.26 bpm, 95% CI –0.48/+0.99, p = 0.49) did not differ significantly between therapeutic CPAP and CPAP withdrawal over the study period of 2 weeks (Table 3).

Treatment Effect on OSA Severity and Daytime Sleepiness

CPAP withdrawal was associated with a return of OSA (between-group change in apnoea-hypopnoea index, +29.4, 95% CI +25.1/+33.7, p < 0.001) accompanied by an increase in daytime sleepiness (between-group change in Epworth Sleepiness Scale score, +2.1, 95% CI +1.2/+2.9, p < 0.001) compared to therapeutic CPAP (Table 4).

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Discussion

This analysis of the effect of CPAP therapy withdrawal on daytime BPV found a slight increase in within-visit variability in systolic office BP in patients with moderate-to-severe OSA. Although our data from several randomised controlled trials have demonstrated this modest effect of recurrence of OSA on short-term variability in *office* BP, it has not found an effect of OSA on short-term variability (morning BPV over 2 weeks) or intermediate-term variability (day-to-day variability over 2 weeks) in *home* BP. Furthermore, the treatment effect on systolic within-visit BPV seems rather modest and presumably is unlikely to be relevant [33].

Using the same trial design, previous CPAP withdrawal studies have found an increase in BP [20, 31, 34] and sympathetic activity [20] and reductions in endothelial function [20, 27, 30] accompanying the return of OSA, indicating a possible pathophysiological explanation for higher BPV. Thus, the marginally accentuated within-visit variability in office systolic BP might mostly be explained by a higher susceptibility to the "white coat" effect [35] as a consequence of an increased sympathetic tone in untreated OSA.

To our knowledge, this is the largest data collection on treatment effects of CPAP therapy on daytime BPV in patients with OSA. Whether the findings regarding short-term therapy withdrawal are comparable to effects of long-term CPAP therapy withdrawal remains uncertain. However, as previously shown [20], even short-term CPAP withdrawal usually leads to a rapid recurrence of OSA and is associated with distinct pathophysiological consequences such as impaired endothelial function, increased urinary catecholamine excretion, and elevation of both BP and HR. Treatment effects of CPAP therapy are often underestimated due to poor patient compliance. Therefore, in our trials, only previously optimally CPAP-adherent patients were randomised to either continue or withdraw from CPAP therapy, and a per-protocol analysis was employed, so that a maximal treatment effect could be expected. Thus, the applied study model can be deemed suitable to evaluate physiological and therapeutic effects on BPV.

Despite convincing pathophysiological concepts linking the effects of OSA and their possible influence on BPV [16, 23, 24, 36], previous trials evaluating the effects of CPAP therapy on BPV have come to contradictory conclusions. Altered BPV has been found in previously untreated and otherwise healthy OSA patients [24]. In a recent uncontrolled prospective study, Pengo et al. [29] investigated changes in within-visit variability in office BP in 78 newly diagnosed patients suffering from severe OSA. The analysis was stratified according to whether patients were hypertensive or not. Hypertensive subjects were not treated with antihypertensive medication either prior to or during the intervention period. Patient data were recorded at baseline and again 2 weeks after initiating CPAP therapy. At follow-up, a reduction of within-visit variability in office systolic BP and HR could be detected, and, while observed in both groups, this reduction was more pronounced in the hypertensive patients, most likely reflecting the effect of CPAP therapy on sympathetic activation. Although in our study the majority of the subjects were diagnosed with hypertension, BP in all participants was well controlled, thus possibly masking a larger effect of CPAP withdrawal on systolic BP variability.

In contrast, a randomised placebo-controlled trial of only 41 OSA patients with a respiratory disturbance index >15/h could not find a beneficial effect from 1 week of CPAP therapy on BPV [28]. Although a higher respiratory disturbance index and elevated urine norepinephrine were positively related to BPV, there was no significant effect due to therapeutic CPAP versus placebo, since BPV declined equally in both study arms. However, all of these studies were based on a rather small study population. Taking into account the existing evidence from the aforementioned trials [24, 28, 29], and adding the results of our analysis of randomised controlled trials, the data suggest that CPAP has at most only a minor effect on daytime BPV.

Although we used standardised BP measurement methods to compile the data presented in our study, there are some possible limiting factors. First, the treatment intervention lasted for only 2 weeks. Secondly, analysis of BPV including home measurements of BP relies on patient compliance. Even though the patients were instructed as to when and how to correctly use the measurement device, there was only limited possibility of ensuring the proper conduct of those measurements. While 24-h ambulatory and beat-to-beat BPV provide different pathophysiological information on daytime BPV [37], standardised visit-to-visit office BPV and day-to-day home BPV have been shown to predict outcome in other patient groups and are an accepted method of assessing BPV [11, 38, 39]. Perhaps most importantly, antihypertensive medication is known to have an effect on BPV which depends on the type of medication. Calcium channel blockers and beta-blockers are commonly used to treat hypertension. However, they seem to have opposite effects on BPV, independently of their general effects on mean BP. In contrast to beta-blockers, calcium channel blockers

have been shown to effectively and consistently reduce BPV [40]. As the patients in this study were asked to continue their medication regimen over the course of the intervention, it is conceivable that despite recurrence of OSA, more distinct changes in BPV may have been masked by medication. In this cohort, all hypertensive subjects were treated, and BP at baseline in these patients was well controlled. On the other hand, whereas in the current study medication was not withheld, in the trial by Bao et al. [28] patients had been taken off antihypertensive medication for 3 weeks prior to the beginning of the study, and still there was no effect of CPAP on BPV.

The results of this study, coming from 4 well-designed randomised controlled trials, provide data regarding CPAP therapy effects on daytime BPV. Despite the lack of evidence of CPAP therapy withdrawal importantly affecting daytime BPV, repetitive *nocturnal* BP surges up to 80 mm Hg seen with OSA due to apnoea- and hypopnoea-associated arousals [41] are abolished by CPAP therapy. Therefore, a long-term beneficial effect on the cardiovascular system from CPAP with regard to BPV may still be possible. Steinhorst et al. [23] recently showed that hypertension is primarily associated with increased night-time BPV rather than daytime BPV. OSA affects cardiovascular regulatory mechanisms most dramatically during sleep, which potentially explains the lack of a strong association between OSA and daytime BPV. The pathophysiology of OSA in hypertension is linked to blunting of the physiological nocturnal dipping pattern of BP and arousal-associated repetitive BP surges, thus possibly having an impact on the development of resistant hypertension in OSA patients [42]. However, the characteristics of BP changes in OSA also include an impaired baroreflex and sustained daytime hypertension, especially in the morning [43, 44]. Consecutively, we expected morning BPV to be affected by the nocturnal consequences of OSA, an assumption that could not entirely be verified. However, since OSA is common, is often coexistent with a cluster of traditional cardiovascular risk factors, and can be effectively treated, an investigation of the preventive effects of CPAP remains a topic for future long-term trials.

In summary, while within-visit variability in systolic BP slightly increased in response to CPAP therapy withdrawal, the clinical relevance of this change is disputable despite a possible blunting effect of antihypertensive drugs on BPV. In conclusion, it is unlikely that OSA contributes to cardiovascular risk via elevated daytime BPV.

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Financial Disclosure and Conflicts of Interest

None of the authors has a competing interest regarding this manuscript.

Author Contributions

Conception and design: all authors; analysis and interpretation of data: E.I.S. and F.L.; drafting of the article: F.L. and E.I.S; revision of the article for important intellectual content and final approval: all authors.

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